AUGUST 1958

Disease-a-Month

Drug Reactions

WALTER S. WOOD
MARK H. LEPPER

THE YEAR BOOK PUBLISHERS • INC.
CHICAGO

DM

Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

RECENT AND FORTHCOMING ISSUES

Joseph H. Burchenal and *Henry D. Diamond*—LEUKEMIA & LYMPHOM

David Davis—DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

Joseph M. Foley and *Simon Horenstein*—CEREBRAL VASCULAR DISEASE

David E. Rogers—STAPHYLOCOCCAL INFECTIONS

George Gee Jackson and *Lowell W. Lapham*—MENINGITIS

Claude E. Welch—DIVERTICULOSIS AND DIVERTICULITIS

Rubin Flocks—KIDNEY STONES

Walter S. Wood and *Mark H. Lepper*—DRUG REACTIONS

Sidney H. Ingbar and *Norbert Freinkel*—HYPOTHYROIDISM

Richard V. Ebert—PULMONARY FAILURE

Franz J. Ingelfinger—DIFFERENTIAL DIAGNOSIS OF JAUNDICE

PRINTED IN U.S.A.

Drug Reactions

WALTER S. WOOD
MARK H. LEPPER

TABLE OF CONTENTS

Walter S. Wood

is Instructor in Preventive Medicine, University of Illinois College of Medicine. During 1956-57 he was a Postdoctoral Fellow in Preventive Medicine of the National Foundation for Infantile Paralysis. In 1953-54 he served as Research Fellow in Medicine and Physician-in-Charge, Municipal Contagious Disease Hospital, Chicago. He received his M.D. degree from Columbia University College of Physicians and Surgeons in 1951. Dr. Wood is a diplomate of the National Board of Medical Examiners and a member of several national and local societies.

Mark H. Lepper

is Professor and Head of the Department of Preventive Medicine, University of Illinois College of Medicine. He received his M.D. degree from George Washington University in 1941. From 1950 to 1952 he was Medical Superintendent, Municipal Contagious Disease Hospital, Chicago. For the two preceding years he was Consultant in Internal Medicine, Walter Reed General Hospital. Dr. Lepper is a Fellow of the American College of Physicians and a member of the American Board of Internal Medicine.

ONE OF THE MOST SIGNIFICANT recent developments in medicine has been the rapid introduction of a great many new drugs for a variety of uses. This has been due to the tremendous efforts of both profit and nonprofit research organizations. The growth of chemotherapy has resulted primarily from the phenomenal success of many new drugs. The results obtained with them have been described as miraculous, wonderful and other "Hollywoodian" terms with some justification. Perhaps the best measure of their merit comes from the physicians who use them.

Twenty years ago most new drugs were looked on with considerable skepticism, and the burden of the proof was on the investigator to establish their worth. Today new drugs are used intensively almost from their introduction, and the burden of the clinical researcher is to try to ascertain the status of a new drug in relation to existing thera-

pies. The tremendous impact of the excessive number of drugs coupled with their relatively uncritical and hasty adoption has been the subject of numerous editorials. As many editors have pointed out, undesirable results follow this unbridled enthusiasm. Chief among these are reactions, illnesses and deaths that occur from using many of the drugs.

Almost every chemical used has been known to produce different undesirable states in a varying proportion of patients. The pleomorphism of drug reactions necessitates their consideration in the differential diagnosis of almost every syndrome occurring in patients who have been receiving drugs. As will be noted, the syndromes caused by most drugs have been documented from empirical observations. In some situations where a mechanism has been demonstrated, the cause and effect relationship is clear. In others, the relation of incidence to dosage suggests a direct cause. In still other situations, the drug is "incriminated" by statistical studies that indicate a greater than expected frequency of a particular syndrome when the drug is being or has recently been used. In many instances, well-controlled statistical studies have not been made, and suspicion rests on the unusual nature of the process or on a general agreement that the syndrome is more frequent than expected from ordinary experience. On the other hand, when the reaction rates are low, only the occasional case report suggests the drug as an etiologic agent. Many case reports are difficult to interpret. The most valuable are those in which the pathologic condition has been precipitated repeatedly by the administration of a certain drug or those in which a confirmatory skin test, serologic test or similar finding has been documented. Numerous case reports lack such evidence for a causal relation and cannot be evaluated, particularly when, as is often true, several drugs have been used. The best that such studies offer is to alert the profession to the possibility of a given type of reaction which should be studied by statistical methods and investigations of possible mechanism. There are, therefore, many potential reactions whose status is not clear and which, on later investigation, are substantiated or denied. When the reaction rate is low, it may be impossible to do more than establish a suspicion. Yet in the individual patient, if a possible cause and effect relation exists, the wise physician had best assume that the drug is at fault and weigh this assumption

in his estimate of the chances of doing good or harm by using the drug.

From these considerations, it seems clear that drug reactions are often suspected that are not verified. Contrarily, it is important to remember that with any drug uncertainty exists as to yet undescribed or unevaluated reactions. As will be seen, the wide variations in pathologic states among patients receiving drugs, added to other individual variations, bring into prominence many effects that are usually not significant. For example, in patients with peptic ulcers, the precipitation of hemorrhages by acetylsalicylic acid illustrates what a drug ordinarily considered to be quite innocuous may do in a patient with underlying disease. The potential, but undescribed, reactions are best thought of as an "X" factor, "X" representing toxicities that are frequent but have been overlooked until the study of new biochemical or physiologic facts brings them to attention. It may represent infrequent toxicities conditioned by the use of other agents, a pathologic state caused by interaction of similar factors. In any event, it is in part the "X" factor that makes the familiar cliché, "It won't do any harm and may do some good," untenable without considerable reservation.

CLASSIFICATION OF TOXICITIES

Table 1 presents a suggested classification to be used as a guide to adverse reactions. It is difficult to define and assign acceptable terminology to uncertain biologic processes. This is particularly true of drug reactions, because widely varied mechanisms occur to produce an even wider scope of reactions, many of which are obscure in pathogenesis.

The toxic effects most clearly understood are those caused by an exaggeration of the drug's principal action. This occurs from using a dose greater than that required, either by miscalculation or deliberately, to obtain a maximal effect. Toxicities from an overdose are most common with drugs such as digitalis, wherein the desired effect requires a dose that can be determined only by assaying the drug in the patient, using minor toxicities or therapeutic effect as the end point. With most drugs, the margin between the amount required to achieve an effect and the amount which seriously exaggerates the action is large enough that this risk is not commonly encountered. A fixed dose on a weight or surface-area

basis minimizes the danger. An undesirable response may result from an exaggerated side action. This is usually construed as an expected but unwanted pharmacologic effect. The difference between side action and the toxic effect resulting from exaggeration of the drug's prime pharmacologic action often cannot be made with precise distinction. Thus, the dry mouth of atropine therapy is considered a side effect but actually signifies that the desired pharmacologic effect has been obtained.

Intolerance may be conceived of as a quantitative deviation whereby less than the usual dose produces an unex-

TABLE 1.—CLASSIFICATION OF TOXICITIES

Overdose
Manifested by exaggeration of principal action
Manifested by exaggeration of a side action
Intolerance
Manifested by patients who develop toxicity with less than average dose
a. Caused by underlying pathology, increased absorption, decreased destruction or excretion
b. "Normal" variation
Paradoxical
Unusual effect usually produced by less than average dose
a. Genetically determined enzymatic defect; idiosyncrasy
b. Caused by underlying pathology
Acquired alteration of capacity to react
Evidence of antibody mechanism
Presumed allergy, but antibody not demonstrated

pected toxic effect in some persons. Patients may be intolerant of or hypersusceptible to a drug's action because the usual pathways involved in the metabolism of the drug have been modified. The patient may have an underlying abnormality that increases absorption, delays destruction or inhibits excretion of the drug. To illustrate, the toxic effects of hexamethonium, the ganglionic blocking agent used in the treatment of hypertension, are caused by an exaggeration of the accepted direct pharmacologic action and result in excessive hypotension, ileus, urinary retention and other parasympatholytic states. The wide range of graded response to hexamethonium occurs because of the marked variability of intestinal absorption. Hence, a patient with delayed intestinal mobility may have a greater than expected effect from a usually acceptable dosage. In a small number of people, there is no explanation for this intol-

erance. It may be ascribed, perhaps in ignorance, to biologic variation. For example, a relatively small, innocuous dose of barbiturate may well cause prolonged somnolence in some persons. Perhaps it is well to perceive that such patients constitute the proportion on the most reactive end of the probability curve.

In contrast, some patients may react paradoxically to barbiturates, manifesting excitement rather than somnolence. Paradoxical effects may be conditioned by underlying pathologic processes in the host but may have no real explanation and are referred to as idiosyncrasies. In some instances, drug idiosyncrasies, similar to intolerances, probably represent biologic variation. On a hereditary basis, one complex of a person's enzyme systems may be exquisitively sensitive to alteration by certain drugs. The antimalarial drug, primaquine, and certain related aniline derivatives such as sulfanilamide best illustrate this principle. These may cause an acute hemolytic anemia in a small percentage of Caucasians and in approximately 10% of American Negroes. This unusual toxic effect has been determined to result from a metabolic defect in the older red blood cells, namely, a reduced glucose 6-phosphate dehydrogenase activity (4).

Some variations in adverse drug responses need not be attributed to normal genetic variation but rather may result from a genetically determined enzymatic defect with variable expressiveness. The latter is partly controlled by environment; in this instance, drug administration.

Idiosyncrasies, such as the one just described, are more frequently an exaggeration of a metabolic side effect and are less commonly related to the desired pharmacologic action. Some overdoses and excessive reactions to a standard dose (intolerance) may be manifested by symptomatology involving systems other than the system at the primary site of action, but idiosyncrasies are more common among side reactions. Only a small percentage of side reactions have been traced to hereditary variability, and unusual drug reactions may occur equally well because of noninherent, acquired alterations. These alterations may be influenced by chronic disease, other drugs, infection or by a variety of metabolic processes. For example, ordinarily the administration of the broad-spectrum antibiotics for several days causes no evidence of significant vitamin depletion. How-

ever, in the presence of severe malnutrition, the deficiency may become obvious, even to producing pellagra.

A significant review of the relation of drug reactions, enzymes and biochemical genetics has recently been published (19).

That reactions to drugs may be conditioned by a multitude of factors is well demonstrated by placebo medication, which invariably elicits a reasonably large number of adverse effects. Thus, psychologic effects may be important in determining the frequency and nature of drug reactions. In addition, the reaction rates in placebo medication seem to be suggested, at least partially, by the investigator, since "stuffy nose" was frequent in the placebo-treated groups in studies in which reserpine was used but not where the effect of penicillin was being studied. Undoubtedly part of this variation indicates simply that symptoms which otherwise would be overlooked are elicited. Placebo studies do give an estimate of the incidence of a symptom in untreated patients, so that a true increase caused by the drug can be measured.

REACTIONS CAUSED BY ACQUIRED ALTERATION OF CAPACITY TO REACT

Allergy is defined as "any specifically acquired alteration in the capacity of living tissue to react. This alteration in capacity to react results from exposure to an exciting agent and is manifest on re-exposure to the same or to an immunologically related agent" (6). The exciting agent is an antigen, and the specifically acquired alteration may, at least conveniently, be interpreted as the formation of antibody. Many allergists would insist that a reaction must be shown to depend on an antibody mechanism before it can be truly considered as allergic. Frequently such definitive evidence is lacking even though an allergic origin is suspected. When this is true there is much room for debate concerning the true nature of the reaction. Drugs, whether acting by antigen-antibody mechanisms or by chemical action, probably exert their effect at a similar level, but there is a paucity of knowledge concerning the chemistry of either effect on the likely substrate, the body's enzyme systems. The difference between the reactions that result from toxic compared to allergic agents is at times obscure. The dis-

tinction may be arbitrary, and is made on the basis of the somewhat equivocal criteria listed in Table 2. A chief reason for suspecting that a drug is capable of producing an allergic effect is by the similarity of the clinical manifestations to syndromes produced in humans by known antigens, e.g., molds, pollens and horse serum. Fortunately, in many in-

TABLE 2.—COMPARISONS OF ALLERGIC AND TOXIC REACTIONS

ALLERGIC REACTIONS	TOXIC REACTIONS
1. Incidence of sensitization correlated with dosage but to a less regular degree. Dose precipitating reaction extremely variable.	1. Usually incidence correlates well with dosage.
2. Not dependent on an overdose.	2. Often a manifestation of an overdose.
3. Generally no relation between pharmacologic properties and symptomatology.	3. Symptomatology often explained by pharmacologic properties.
4. Often drugs with similar chemical configuration will immediately precipitate a reaction, even if the second drug has no known similar pharmacologic action.	4. Drugs with similar chemical configuration only active if there are similar pharmacologic properties and a full dose is required.
5. Occurrence of the reaction is late, during or following first course of drug, or may be immediate on second or later course. (Indicate time for antibody formation.)	5. Occurrence of reaction related to accumulation of drug. Rarely occurs after drug has been stopped or immediately when drug is readministered.
6. Repetition of effect on re-exposure to drug, often with less than therapeutic dose.	6. Repetition of effect on re-exposure usually with greater than therapeutic dose of drug.
7. Antiallergic therapy such as antihistaminics often effective.	7. Antiallergic therapy usually of no avail.

stances, drug allergy has been confirmed by demonstrating the occurrence of an antibody-antigen reaction by various methods, to be discussed subsequently. The similarity of the reaction in which antibodies have been demonstrated to those in which they have not lends evidence to the possibility that the latter also are dependent on antibodies. Moreover, a drug suspected of producing a specific allergic, rather than toxic, effect in some instances has been shown adequately to sensitize experimental animals.

TYPES OF ALLERGIC REACTIONS

Many drug reactions do not fulfill the criteria suggested for the classic allergic reaction yet have certain character-

istics that suggest an immune mechanism, or hypersensitivity. The hypersensitive state includes the immediate reactions, such as anaphylaxis, Arthus's phenomenon and the atopic reactions (asthma, serum sickness and some instance of urticaria). In addition, the delayed type of hypersensitivity may occur following drug administration under certain conditions. Usually the delayed type of reaction occurs after dermal sensitization, as exemplified by contact dermatitis. The appearance of the delayed type of sensitization to a drug does not exclude the simultaneous development of immediate types. The immediate may be grossly differentiated from the delayed type by several characteristics of the latter: (1) special requirements for sensitization, e.g., usually simple chemical compounds of an irritating nature contact the integument and combine irreversibly with proteins derived from the body, mainly the skin, (2) lack of relation to humoral antibodies and presence of antibodies in cells, (3) a delay of 24-72 hours usually occurs before the reaction is manifested and (4) evidence of a wide spectrum of cellular types involved in the reactions contrasted with the immediate type, which is essentially limited to smooth muscle, vascular endothelium and collagen. Unfortunately, the term delayed has also been used to describe certain reactions of the immediate type such as serum sickness and delayed urticaria. Even though these reactions may not become clinically obvious for many days after exhibition of the drug, the actual reactions probably begin immediately after union of antibody and antigen. The delay probably is the time required to form antibodies. "Late immediate reactions" is a better term for these reactions.

The nature of an allergic drug reaction is determined by the body tissues and/or enzyme systems that are disturbed. If it is limited to the skin or restricted to certain shock organs not involved in globulin production, circulating antibodies need not be demonstrable. If, in addition, the determinate group of a drug, an antigen, affects enzyme systems of tissues involved in globulin synthesis, then humoral antibodies may, under certain circumstances, be demonstrable and capable of being passively transferred with the serum (23).

ANTIGENIC PROPERTY OF DRUGS

Most drugs, because of their small molecular size, are incapable by themselves of directly inducing the allergic state and antibody formation. In experimental animals, generally, only proteins of large molecular weight are completely antigenic, although some complexes of lipocarbohydrate and a few high molecular weight polysaccharides share in this capacity. Simple substances of low molecular weight, such as most drugs, are effective as haptens that combine with body proteins and thereby act as complete antigens in the potentially reactive tissues. Extensive experimental studies have been performed to determine the sensitizing capacity of a diverse group of chemicals and drugs. Numerous chemicals known to be responsible for the so-called allergic diseases are capable of sensitizing laboratory animals, producing manifestations of anaphylaxis (10). As the hapten determines the specificity of the antigen, a group of drugs sharing an identical basic structure and reactive groups may be expected to have similar antigenicity, or cross-reactivity.

On the other hand, a subtle alteration may significantly alter the antigenicity. Azoproteins produced by the conjugation of a diazonium salt of a simple chemical with various proteins, when injected into a rabbit, will produce circulating antibodies. The diazonium salt is made antigenic by attachment to a protein. The antibodies produced against several different proteins combined with the same hapten will cross-react, usually incompletely. Although the simple hapten cannot by itself induce sensitization, the antibody, formed in response to its conjugation product with protein, is capable of combining with the hapten in the unconjugated state. The capacity of a drug to link with a tissue protein and to be recognized as a substance foreign to the body depends on the presence of reactive groups.

Certain structures are recognized as relatively more capable of inducing antigenicity. Thus the benzene ring with a labile NH_2 group ("benzamine"), occurring in the sulfonamides, is such a configuration which yields a high incidence of drug reaction. Although drugs that contain chemical groupings such as carboxyl, amino and hydroxyl are known to cause hypersensitivity with particular ease (11), any

drug of simple molecular structure, including the heavy metals, should be considered a potential hapten. Unless it is completely inert, a foreign substance introduced into a living organism will react with and cause modification of protein molecules and host metabolic systems. Such inert substances are rare. It is not possible to predict the toxicity or allergenicity of a pharmacologically active drug with certainty. A metabolic by-product of the drug may be the effectual hapten. A wide variety of drugs and chemically useful agents containing aromatic amino or nitro groups may be metabolized easily by active cellular processes to form more reactive intermediates. For example, a wide group of amines, nitro compounds, azodyes, sulfonamides and other para-aminobenzoic acid derivatives are metabolized to form compounds of quinone structure. The quinones have a high affinity for proteins and are associated thereby with a high sensitizing power (16). Aromatic amino derivatives capable of linkage with proteins often cause a delayed contact-type reaction in experimental animals but can sensitize appropriate tissues to cause systemic allergies.

Even though most drug reactions subside promptly when administration of the agent is discontinued, symptoms may persist for a long period. Attention has been called to this phenomenon by the frequency of such reactions with the use of penicillin. Actually a small percentage of penicillin reactions follow this course but, because many patients receive penicillin, the absolute number is large enough that these reactions are often seen. A similar sequence may follow the use of other drugs as well. The explanation for this sequence is not clear. It has been hypothesized that in these patients the drug or a metabolic product of it leads to sufficient alteration of the host protein, by conjugation or otherwise, to stimulate antibody formation.

Once this occurs, the reaction can continue as long as the abnormal protein or a protein with sufficient serologic overlap continues to be produced. If such a state is postulated, it is not necessary for the inciting drug to remain linked to tissue protein to perpetuate the immune mechanism. However, there are experimental studies indicating that some antigens and drugs remain in the reticuloendothelial cells for a long period. The implication is that at least some of the persistent reactions may be related to the presence of drug in the tissues. Carefully controlled studies

with penicillinase in this syndrome may indicate whether the destruction of traces of penicillin is important and whether it terminates this kind of reaction.

Closely related is the evidence of hypersensitivity of patients even though they may be symptom-free for long periods. The persistence of the basic allergic state is indicated by the immediate reaction when the drug is readministered. Some of the immediate anaphylactic reactions to penicillin and serum in persons who previously had only mild urticaria as a reaction are convincing evidence of persistence of antibodies in the tissues, even if they are not definitely circulating. The more severe and accelerated serum sickness-like reactions, with incubation periods of only a few hours or days, occurring after the administration of penicillin in a patient who previously reacted can be interpreted as indicating a stepped-up antibody response. This response is similar to that in accelerated serum sickness.

The difference between hypersensitivity and toxicity may not be great. In both situations altered metabolic states are basic. If hypersensitivity is limited by definition to those states in which antibodies, either circulating or fixed to cells, have been demonstrated, it can be considered part of the general classification of toxic reactions in which a specific mechanism has been described. However, the antigen-antibody reaction initiates such a long chain of similar processes, regardless of the nature of the initiating antigen, that the pathologic end results are practically identical with many different compounds. This fact sets allergic reactions apart from the other toxicities in which there is a more immediate effect on the metabolism more dependent on the structural configuration of the drug. It is possible that there may be other processes that activate a similar "final common path" and, therefore, there may be marked similarity of clinical manifestations with diverse drugs without an antigen-antibody reaction. For example, many drugs interfere with the hemostatic mechanisms, thereby causing hemorrhagic disease. These are considered toxicities and not allergenics, because the mechanism is understood and because antibodies are not involved. Similarly, the clinical syndromes resulting from disturbed function of the lower motor neurons are identical, regardless of inciting agent or mechanism. However, since the biochemical and biophysical changes

in many of these situations are unknown, a precise classification is not possible and the broader term, toxicity, is generally used.

A good example of this difficulty is the impossibility, with current measuring devices, to determine whether the mechanism in aplastic anemia resulting from chloramphenicol involves an immune reaction or toxicity. It does fulfill many criteria ascribed to allergic processes, yet there are no available tests demonstrating that antibodies in the classic sense are involved.

Despite these less apparent and basic similarities, it is wise to distinguish between the various types of drug reactions, using available clinical and laboratory tools. There are often practical implications. Thus reactions known to depend on antibody mechanisms make further use of the drug dangerous, whereas some dose-related toxicities require only a lower dose. Moreover, therapy in allergic-type reactions is directed toward the "final common path," activated by the antigen-antibody reaction and therefore is process, and not drug, specific.

CLINICAL MANIFESTATIONS OF REACTIONS

In the following descriptions emphasis will be placed on the syndromes known to depend on antibody mechanisms. Included are many reactions for which no mechanism has been documented but which, because of clinical similarity to proved allergic reactions, are accepted as such. Also, other toxic reactions of unknown pathogenesis or of differential diagnostic importance are included.

The classic frame of reference for allergic reactions of the immediate type is the syndrome of serum sickness. An excellent review of this subject is given by Kojis (9). This disease begins within 14 days after the first dose of serum in 95% of patients. In 75%, the incubation period is from 5 to 10 days. When serum is administered a second time, the incubation period is generally shorter and the reaction more intense—a condition known as accelerated serum sickness. Anaphylaxis appears as the extreme limit of acceleration and accentuation manifested when serum is readministered, particularly in patients who have reacted previously. In this state, the incubation is seconds to minutes, and the intensity is such that death frequently occurs.

The most common manifestations in the complete clinical picture of serum sickness are fever, rash, edema, lymphadenopathy, arthralgia and neuritis. Fever may be as high as 105 F. and may precede the other manifestations. Although 80% of the rashes are urticarial, they may be erythematous, morbilliform, petechial, purpuric or a combination of these. Edema is frequently associated with the skin manifestations but may precede them. It is generally most severe around the site of injection and in the usual distribution of angioedema, namely, of the lips, periorbital regions, hands and feet. However, it can occur in any soft tissue, including the viscera. It is particularly dangerous where it threatens to obstruct the airway. Arthralgia is the usual finding, but occasionally actual arthritis exists with inflammation sufficient to allow accumulation of fluid containing many lymphocytes and a few granulocytes.

Visceral lesions include lymphadenopathy in 90% of patients and splenomegaly is common. Edema of the brain and peripheral nerves leads to a multitude of syndromes. The most common is peripheral neuritis, particularly of the brachial plexus. Stupor, convulsions, hallucinations, meningismus, hemiplegia and paraplegia all have occurred. Other visceral lesions are infrequent, although albuminuria and cylindruria are common and oliguria and suppressed renal function rare. Clinical evidence of myocardial involvement is quite rare.

Eighty-eight per cent of patients with serum sickness recover within 4 days.

Although the foregoing description indicates that serum sickness presents a fairly uniform disease picture caused by serum, there is considerable pleomorphism. Thus the skin manifestations may be out of proportion to the others in the syndrome, and fever may occur as the only manifestation. In fact, all the symptoms and signs mentioned can occur singly or in any combination, in addition to some of the more unusual ones. There is no satisfactory explanation for the different clinical pictures. Even though the disease seems to be equivalent to that of animal sensitization, humoral antibodies are not always demonstrated. Moreover, antibodies are demonstrable in many patients who have received serum but who never have become ill. It is likely that there are many conditioning factors that determine the clinical picture as well as its frequency. The differences in

quality of antigen may be important, since some samples of horse serum are more active than others. More important, probably, are quantitative, and perhaps qualitative, differences in the antibodies produced by different hosts and their varied affinity for tissue localization.

As will be seen, many drug reactions are similar to those of serum sickness both in temporal relation and clinical manifestations. In most of these, however, the demonstration of antibodies has been much less successful and the pathogenesis of the lesions even less certain.

The frame of reference for reactions caused by the delayed type of hypersensitivity is contact sensitization of the skin in animals and contact dermatitis in man. Some visceral and systemic manifestations of drug reactions may well be dependent on this type of sensitization, but the tools for demonstrating antibodies, except in the skin, are rudimentary.

Skin Reactions

Dermatitis is the most common expression of drug reactions, and the types of skin lesions induced by drugs are legion. Both immediate and delayed types of hypersensitization are involved alone or together in a reaction. Contact dermatitis, also referred to as dermatitis venenata and eczematous dermatitis, is the most common skin reaction. No humoral antibodies are demonstrable by passive transfer of serum, such as the Prausnitz-Küstner reaction, but passive transfer has been demonstrated experimentally using white blood cells. Moreover, application of the antigen on the skin, as a patch test, can produce a vesicular reaction that occurs maximally at 24-48 hours. When these phenomena are demonstrated, they indicate a delayed type of hypersensitivity. Not all contact-type dermatitis need be of allergic origin, so that failure to demonstrate antibodies may indicate another mechanism instead of just failure to find antibodies. Contact dermatitis is produced by repeated exposure of the skin to the offending agent—usually a drug of simple molecular structure. Sensitization is facilitated by abraded, or broken skin. This type of skin involvement is particularly common in persons frequently exposed to topical application of a drug, such as patients with underlying skin disease. Contact dermatitis is, therefore, too often an example of

iatrogenic disease. In addition, the incidence of contact dermatitis is excessive in persons engaged in the manufacture or dispensing of drugs. For instance, nurses have a high incidence of dermatitis from handling streptomycin and penicillin. Although this type of reaction is induced by topical application of the drug, potentiation or exacerbation can occur when the same drug or one with similar structure is ingested. The characteristic lesion involves the epidermis primarily and consists of erythema and vesiculation with pruritus. Often it is initially localized to the area of drug contact. The acute lesion can become secondarily infected and if a wide skin area is affected significant systemic illness may result. As the lesion becomes chronic, the skin becomes eczematous. A similar dermatitis can result from initial internal administration of a drug, and the eruption is usually more generally distributed. The patch test elicits a positive delayed reaction less regularly in the eczematous reactions that follow ingestion or injection.

Local or fixed eruptions can follow parenteral and oral administration. On occasion, the reaction occurs in a site previously sensitized by topical application of the same drug or one of similar structure. More often the reason for a localized eruption following systemic administration remains obscure.

The id eruption is another skin rash generally considered to be a delayed type of hypersensitivity. It is similar to the id reaction of epidermophytosis, which consists of a vesicular, oozing, erythematous, pruritic and, sometimes, eczematoid rash involving the groin and interdigital spaces. The reaction occurs most frequently following penicillin, often within 24 hours after onset of therapy. There is no known explanation of the pathogenesis of the id reaction to penicillin, although several have been proposed. Because of the short incubation period, it has been suggested that id reactions occur because of a prior sensitization. Some have attributed the rash to antigenic cross-reaction between trichophytin and penicillin. The best evidence for such a relation is clinical. Both the nature and distribution of the penicillin-induced lesions are practically identical with those seen in the id reaction to trichophytosis. In addition, positive delayed reaction to skin tests to both trichophytin and penicillin frequently occur in persons who manifest an id reaction to penicillin. Controlled studies have revealed no

significant correlation to substantiate this cross-reaction (18). The penicillium mold also has been suggested as the sensitizer. The postulation of earlier sensitization by the penicillium mold with subsequent cross-reaction to the crystalline drug preparations is attractive. Although it would explain many reactions to the drug where previous exposure is denied, there is no sound evidence that this mechanism actually occurs. In fact, skin tests with penicillium do not support the claim.

Erythema nodosum is another rash that may well be a delayed type of allergic reaction. Many drugs including sulfathiazole cause this lesion in addition to infections. Antibody mechanisms have not been proved in most instances. But with sulfathiazole the 5-10-day incubation period, when the patient is first exposed to the drug contrasted with its precipitation by a single minute dose once the patient has reacted, suggests an allergic mechanism. Moreover, with sulfathiazole the erythema nodosum may occur as part of a syndrome that is otherwise similar to the other sulfonamide reactions.

It is thought that contact dermatitis, the id reaction and erythema nodosum may indicate delayed hypersensitivity (22).

As already indicated, the manifestations of serum sickness are believed to represent the pathologic changes associated in humans with an immediate type of allergic reaction. At least the major alterations such as urticaria are therefore considered to depend on this pathogenesis. Therefore, urticaria can be thought of as the typical sign evoked in immediate-type reactions when an antigen or a hapten such as a drug is injected into the skin and combines with antibody. In addition, it may result from a variety of physical and chemical stimuli in the skin, including an antibody-antigen reaction, a physical force (heat, cold) or even mechanical pressure (dermatographia).

A common physiologic and/or biochemical mechanism is probably activated with any of these agents. The lesion of urticaria is pathologically identical, whether it is caused by one of the foregoing factors or by an injection of histamine or histamine liberator into the skin. Both histamine and proteases are released in allergic urticaria as the direct or indirect result of the union of antibody and antigen. This is considered characteristic of all immediate-type allergies.

Although urticaria is characteristic of skin tests in the immediate type of hypersensitivities, it does not follow that drug reactions eliciting urticaria must represent hypersensitivity of the immediate type. For example, patients with urticarial rashes from drugs often do not demonstrate the immediate-type skin reactions. Passive transfer of their sera also fails to reveal evidence of antibody. A drug given therapeutically that does elicit urticaria with demonstrable circulating antibodies may not be the same antigen, conjugated in the same manner, when injected intradermally.

For these reasons, skin testing and serum transfer tests in patients with urticarial skin reactions following drug administration often have little practical application. The wheal of urticaria, regardless of pathogenesis, consists of a localized area of edema and erythema resulting from dilatation and increased permeability of the underlying skin vessels. Angioedema may be considered to be an exaggeration of urticaria wherein the edema is of more significant magnitude and consequence. Urticaria may persist only for an hour or less or for a long time. Thus, even urticaria, a hallmark of the immediate type of allergic skin reaction and of serum sickness, is not necessarily caused by allergic reactions and likely not always even by histamine.

The mechanism of many other skin reactions is even less clear. This can be explained by the wide discrepancy between morphology and pathogenesis. Penicillin can cause a minimally detectable area of erythema scattered over a small area or it can cause a severe generalized and diffuse hemorrhagic bullous eruption. The two eruptions may have a similar basic mechanism. On the other hand, numerous drugs can cause the identical lesion and not necessarily be pathogenically related. Erythema of the face may be a pharmacologic side reaction of atropine, contact dermatitis related to cosmetics, direct irritation from soaps or eruption from changes in the dermis caused by many agents and probably dependent on an underlying allergic reaction.

A wide variety of drugs including penicillin, streptomycin, novobiocin, para-aminosalicylic acid, the barbiturates and sulfonamides produce simple or multiple patterns of exanthematous eruptions which consist of the papular, macular, morbilliform, scarlatiniform and erythematous types. In the severe forms, most of these drugs may produce exfoliative dermatitis, but this reaction is much less frequent, even if

the administration of the drug is not stopped. The pathogenesis of the exanthematous reactions is no less diverse, and perhaps more obscure, than is that of urticaria. Even in the serum-sickness syndrome the pathogenesis of many of these manifestations is not clear. Therefore, it is not known which of these are allergic reactions of the immediate or delayed type and which are initiated by other mechanisms. However, the incubation period the first time a drug is administered and an accelerated effect with a minimal dose once the patient has reacted or has been treated previously without reaction, suggest an allergic mechanism. Some drugs cause a predominant manifestation, even though most drugs that cause many cutaneous reactions can produce almost any urticarial or erythematous lesions. Thus, the sulfonamide rash is characteristically morbilliform but scarlatiniform, erythema multiforme and purpuric reactions occur. Novobiocin reactions are similar, but penicillin causes urticaria and scarlatiniform rashes most commonly, and morbilliform infrequently. The infrequency with which antibodies and positive skin tests are found in these reactions is noteworthy.

A workable concept of the relation between the erythematous rashes, whether precipitated by antigen-antibody or other mechanisms, would be to relate them to the general problem of vascular reactions of the skin. Whereas dermatitis venenata has been considered a process primarily of the epidermis, urticaria and the exanthematous eruptions chiefly involve the blood vessels and connective tissue of the dermis (3). If the dermal blood vessels are injured, whether by antibody-antigen reaction, toxin or mechanical trauma, various combinations of edema, hyperemia, diapedesis and/or extravasation may result, depending on the type and severity of the insult. In some instances, the reaction may be similar to the triple response noted by Lewis, ascribed to the release of a histamine-like substance in response to local skin trauma; initial erythema, a wheal of edema and, finally, a flare of spreading erythema. The macular, morbilliform and scarlatiniform eruptions may be primarily vascular dilatation, the flare and diapedesis in varied degrees of severity and distribution.

If greater vascular injury occurs with extravasation of red blood cells, purpura will result. If extravasation occurs into an area of intense exudation and edema, the result could

mimic the hemorrhagic bullous eruptions seen after taking such drugs as the iodides, barbiturates, anticonvulsants, sulfonamides and penicillin. It is possible that some eruptions caused by drug toxicity and resembling erythema multiforme involve a triple-response mechanism. Erythema multiforme-like eruptions have followed administration of drugs including the sulfonamides, salicylates, barbiturates, penicillin and aminopyrine. The marked and diffuse erythema seen in early exfoliative dermatitis is consistent with a widespread flare. Urticarial and exanthematous drug reactions may progress to erythroderma and exfoliation. Whether it is a concomitant of constitutional disease or follows drug administration, exfoliative dermatitis is a clinical entity and not one that necessarily results from a single type of insult. It is possible that several different types of immune and/or toxic mechanisms are involved concomitantly in any of these reactions.

The purpura of drug reactions as well as some purpuras that develop with apparent spontaneity may result from injury to the vessel wall or platelets. Either of these mechanisms may be a manifestation of toxicity, hypersensitivity or both. Purpura can occur as the direct toxic effect of a drug such as ergot, as the result of an antigen-antibody reaction or, perhaps, as a manifestation of the Shwartzman reaction (24). None of the urticarial, exanthematous or purpuric skin eruptions resulting from drugs can be definitively assigned to allergy. Immediate or less commonly delayed skin tests may be elicited and antibodies demonstrated by various technics under certain in vitro conditions. However, the correlation is inadequate, and, even if positive, usually cannot be interpreted as conclusive evidence of a cause and effect relation. Elimination and provocative tests as used in the known allergic disorders occasionally may be of diagnostic assistance, but the latter method should be reserved for the most critical circumstance, if used at all.

Systemic Reactions

Systemic reactions to drugs are more diverse and complicated than are those primarily involving the skin. Almost every toxic drug reaction is reflected by general symptomatology, even when a single-organ system is principally involved.

Even among the reactions usually considered allergic in origin, just as with serum sickness, the skin manifestations may occur alone, although usually they are accompanied by multisystem disease. For example, drug-induced erythema multiforme bullosum frequently is accompanied by serious toxicity, and arsenical erythroderma may be fatal. Moreover, the systemic symptoms occur without a skin rash and may vary from fever alone to a more complex illness. The subsequent discussion of systemic reactions will consider several more common or intriguing conditions in which an allergic mechanism has been shown or is thought to play a role.

Anaphylaxis is a relatively common, severe reaction which apparently has increased in frequency for the most part because of the extreme use and abuse of penicillin. It has been estimated that over 50% of people in the United States have received penicillin at least once. An accurate incidence of anaphylaxis following the use of penicillin or any drug other than serum is not available, because of the inadequacies of data on the frequency of drug usage. Probably well over 100 patients will have a significant anaphylactic reaction to penicillin every year. About 5% of reactions to penicillin are anaphylactic and of these about 25% will be fatal. Anaphylactic reactions generally are thought to occur more frequently in atopic persons. This need not imply that sensitization of atopic persons is more frequent, although statements to that effect have been made. It is perhaps more likely that the patient with hay fever or asthma is predisposed to react more violently once sensitized. Either or both explanations may be true. Anaphylaxis is the classic example of the immediate type of hypersensitivity. Circulating reactive antibodies are present and immediate-type skin tests usually can be demonstrated when elicited at the proper time. Tests performed previous to anaphylaxis usually elicit a wheal whereas those performed after the reaction has occurred are more often negative. The latter may be erroneously interpreted as indicating that the patient's sudden collapse was caused by another mechanism. False negative skin tests occur in patients being treated with penicillin as well as with other allergens. Furthermore, a positive skin test does not necessarily indicate that the patient will react with anaphylaxis. It does show, however, that the patient's skin is sensitized and that this may signify systemic sensitization. Also, it indicates that the patient is capable of

having a systemic reaction, if the drug is given by any route. It is essential to realize the significance of the latter!

Compared with patients who develop other types of reaction from penicillin, those who react anaphylactically more often have a history of a previous untoward reaction. The history is the most helpful way to determine the potential reactor to penicillin as well as to any other drug or chemical compound. Often anaphylaxis to serum and occasionally to penicillin will occur with no antecedent history of exposure. With serum, the cross-reaction is with horse dander. Similarly, there are various mechanisms whereby exposure and sensitization may occur unbeknown to the patient. For example, sensitization to penicillin theoretically can be induced by the presence of the antibiotic in milk. Certainly more significant is the almost universal failure of physicians to tell patients what medications they have received. The acute anaphylactic reaction occurs within 20 minutes after administering the drug. It is initiated by a feeling of anxiety and faintness and, unless therapeutic measures are immediately taken, progresses rapidly to severe bronchospasm with cardiovascular collapse.

Minute amounts of antigen can evoke anaphylaxis. An instance has been reported of anaphylaxis following application of penicillin eye ointment. It has followed intracutaneous penicillin tests, although this instance should not be interpreted as an additional factor nullifying their value. It is possible to have an anaphylactic reaction to penicillin immediately following an injection of a completely unrelated drug. One explanation for this is the presence of penicillin in contaminated syringes.

The syndrome of serum sickness can follow the use of a large number of drugs including most of the antibiotics, many of the chemotherapeutic agents, the barbiturates and, of course, serum. Penicillin has displaced serum as the most common etiologic agent, principally because it has largely replaced serum therapy. The incidence of serum sickness from penicillin based on the number of patients treated is much less than that for serum. There is no essential difference between serum sickness that may follow the use of serum and that which may follow penicillin treatment. In penicillin reactions, lymphadenopathy and splenomegaly are less common; otherwise the major manifestations are similar to those just described for serum sickness.

The more bizarre manifestations, such as erythema multiforme, morbilliform rashes, purpura, "toxic-nephritis" and peripheral neuritis are less common in penicillin reactions. The reaction may occur 3-30 days following drug administration, and an incubation period of more than 14 days is more frequent than where serum is used. As with anaphylaxis, serum sickness usually follows the ingestion or injection of a drug, but it may occur also following topical application. It is much more difficult to establish the presence of an immune mechanism by the demonstration of humoral antibodies and/or a positive skin test in this reaction than it is in anaphylaxis from penicillin. Both positive, immediate and delayed, as well as negative reactions from skin tests have been reported antecedent to, during and after the reaction. Serum sickness cannot be predicted either by a positive or negative reaction to a test, and these tests are of no clinical value in this type of reaction, at least with current methods. Among drug reactions, those caused by penicillin more nearly simulate serum sickness. The systemic reactions to sulfonamides, antithyroid drugs, anticonvulsants and other drugs have many features of serum sickness, although an unusual feature is usually predominant and the classic picture, infrequent.

Among the more severe generalized illnesses believed to be caused by drugs are disseminated lupus erythematosus and periarteritis nodosa. Lesions suggesting the latter disease have been produced in experimental animals by administering serum. L. erythematosus cells, indistinguishable from those found in the idiopathic disease, have been found in penicillin reactions. Moreover, a lupus-like syndrome has followed treatment with hydralazine (Apresoline®) and some sulfonamides. The reactions are characteristically reversible contrasted with those of the spontaneous idiopathic disease. The question arises whether the paucity of cells does not distinguish these conditions from the true disease. As distinct from serum sickness, there is little insight into the mechanism, although it is likely that a type of immunologic hypersensitivity is involved. It is noteworthy that the incidence of lupus erythematosus has increased since the use of penicillin, and the incidence of periarteritis, since the introduction of serum and sulfonamide therapy.

The use of sulfonamides, and less commonly penicillin, has been reported to be complicated by a disease resembling

periarteritis nodosa. The course is typically more acute and fulminating, and the distribution of vascular lesions is dissimilar to those of the classic disease. Some authors have preferred to use the term "acute necrotizing angiitis" to describe the process that may follow treatment with these drugs (8). It is possible that this form of systemic vasculitis is a more severe manifestation but is related pathogenically to some of the dermal drug reactions previously discussed.

Visceral Reactions

The viscera can be injured by processes that suggest hypersensitivity as well as by the more obvious and common directly toxic effect. Evidence for an immunologic mechanism in most instances is involved, complex, uncertain or completely lacking. Many such reactions are nonspecific and secondary, but in some instances an organ or organ system may be the "shock organ" of an antigen-antibody reaction. The diffuse early degenerative and inflammatory changes seen in the liver, spleen, lymph nodes, kidney and heart in patients who succumb to anaphylaxis are believed to be nonspecific and related to anoxia. Exfoliative dermatitis of any etiology may have wide-spread repercussions in the viscera; for example, a concomitant nephritis may dominate the clinical picture.

Hepatic involvement.—Hepatic damage occurs relatively often as a direct toxic effect of numerous drugs. This should be expected in an organ with such a plethora of delicate enzyme systems. Chlortetracycline is directly toxic to the liver, as seen clinically when excessive intravenous dosages are used. Significant hepatitis also has followed administration of sulfanilamide, penicillin, streptomycin, phenylbutazone and isoniazid, to name a few. Acute diffuse hepatic necrosis has been reported in a child who received novobiocin. This antibiotic also may cause a benign pigmentation of the skin and sclera thought to be a bilirubin derivative pigment. Both icteric and anicteric hepatitis have occurred with the use of para-aminosalicylic acid, chlorpromazine and methyltestosterone. In these patients jaundice associated with chills and fever can mimic an infectious intrahepatic obstructive cholangiolitis. Even an associated urticaria or one of the exanthematous rashes does not rule

out hepatitis. Although by no means adequately demonstrated, an allergic mechanism is thought by some to be involved, since the dose reaction curve is not so consistent as in most toxicities, and second courses occasionally make the condition reappear. Eosinophils may be present in the tissues, granted that their presence does not necessarily indicate allergy.

RENAL INVOLVEMENT.—In excessive dosage, many drugs are directly toxic to the kidneys, and toxic nephropathies have followed the use of a large number of drugs, including many antibiotics and chemotherapeutic compounds. Any drug that produces a vascular collapse may lead indirectly to acute renal failure of the type frequently seen after most shock-like states. The renal lesion following anaphylaxis, therefore, may be mainly a nonspecific reaction to shock rather than damage to the kidney per se by the antigen-antibody initiated mechanism.

However, as previously mentioned, evidence of renal involvement with albuminuria and cylindruria is seen frequently in serum sickness and in drug-induced diseases of a similar type. In addition, patients and animals who develop hypersensitivity angiitis usually have a renal lesion, probably dependent on an immune mechanism. Occasionally, the only manifestation is found in the kidney. Sulfathiazole produces a peculiar inflammatory lesion of the kidneys and liver associated with crystals of the drug in the tissues. Nephritis caused by the sulfonamides must be distinguished from the mechanical damage to the urinary tract and kidney from insoluble sulfonamide derivatives, since the latter are controlled by keeping the urine alkaline and of sufficient volume.

Evidence of renal impairment occurs in some tuberculous patients treated with para-aminosalicylic acid and streptomycin.

CENTRAL NERVOUS SYSTEM REACTIONS

Manifestations of drug toxicity of the nervous system can range from the momentary irritating effects of intramuscularly administered drugs to transverse myelitis or psychosis. There are, fortunately, few examples of allergic manifestations to drugs in which the central nervous system is a primary shock tissue, although the acute demyelinating disease that follows the injection of rabies vaccine is apparently an

example of specific hypersensitivity. More commonly the central nervous system reactions result from direct toxic effects or are part of a more generalized hypersensitivity reaction.

A few of these will be described briefly. Most therapeutic agents administered by the intrathecal route are irritating and can have serious consequence. Convulsions, arachnoiditis, peripheral neuritis, transverse myelitis and coma occasionally follow intrathecal penicillin or streptomycin; headache, nausea and vomiting are common. Streptomycin and dihydrostreptomycin are well known for their toxic effects on the 8th cranial nerve. Polymyxin B may cause paresthesias as well as transient ataxia. Frank psychosis has been reported with all the antibiotics as well as with the sulfonamides and isoniazid. It is often impossible to attribute the psychosis to the drug rather than to the underlying disease.

Cycloserine, a tuberculostatic drug, thus far used only on an experimental basis in man, has caused such frequent and severe psychic disturbances and convulsions that its use will be limited. A serous type of meningoencephalitis may follow the use of para-aminosalicylic acid alone and in combination with streptomycin and/or isoniazid in patients with tuberculosis. Thus a hypersensitivity mechanism is suspected. Isoniazid has caused a number of significant neurotoxic effects including diplopia, vertigo, paresthesias, hyperreflexia, mood defects and optic atrophy. Evidence suggests that pyridoxine may be beneficial in preventing these complications. The antihypertensive drug, mecamylamine, in addition to producing untoward effects by an exaggeration of its desired pharmacologic action produced by ganglionic blockade, may cause coarse tremor, agitation, hyperreflexia and other gross neurologic defects. Meprobamate, one of the recent tranquilizing "wonder drugs," may produce potent neuropsychic effects in addition to its desired action. Severe depression or, paradoxically, extreme excitation may occur. Rare instances of extraoccular palsy and generalized muscle paralysis have followed the use of this drug. These effects probably are related to its pharmacologic properties and not allergy, since hypersensitivity to the drug is apparently most unusual, although urticaria and purpura are known.

An unusual but frightening immediate reaction can follow the accidental intravenous administration of procaine penicillin. The patient has tachycardia, sweating, anxiety, irregu-

lar respiration, blurred vision, dizziness and paresthesias. The reaction, similar in duration to an anaphylactic reaction, may be confused with it. These effects are presumed to be secondary to the action of the contained procaine on the central nervous system (14), although the insoluble nature of the material injected may well be important in the pathogenesis.

Pulmonary Involvement

Bronchial asthma is the most common and clinically significant reaction of the pulmonary tissue to drugs. This is usually construed to result from an immune mechanism of the immediate type, although many of the same problems discussed under urticaria apply here.

Deaths still occur when patients with bronchial asthma are treated with aspirin. The sudden reaction with relatively small doses has led some to consider the phenomenon as a hypersensitivity mechanism; however, this has not been demonstrated conclusively. It should be recalled that morphine can and often does have dire consequences when used in asthmatic patients. The effects of morphine are bronchospasm and respiratory depression, both expected from its known pharmacologic actions.

Fibrinous pneumonia has occurred during the treatment of malignant hypertension with methonium salts. Numerous cases of a fleeting pneumonia have been reported with para-aminosalicylic acid, some of which have been associated with eosinophilia (Löffler's syndrome). In the latter, a hypersensitivity mechanism is believed to be involved because of concomitant symptomatology and by analogy with a similar condition accompanying allergic asthma.

Reactions Involving Blood Cells and Platelets

As with other systems, the mechanisms of induced drug reactions affecting blood cells and platelets are multiple: (1) metabolic defects in which the cell is hypersusceptible to enzymatic interference and which may be genetically controlled, (2) direct toxic effects on the cell and (3) immunologic phenomena. Examples of these are: (1) prima-

quine toxicity to the red cells, (2) nitrogen mustard and (3) quinidine. In addition, an adverse effect can result from a combination of these basic mechanisms. This system differs considerably from those previously discussed, in that the blood cells are more easily studied. They are uniquely available for biochemical and immunologic analysis and serve as a useful tool in the comprehension of drug reactions. The blood dyscrasias consequent to drug administration are too multiple and complex to discuss in detail. This particular subject has become a specialty in itself. The major dyscrasias will be mentioned with a few examples of each.

1. *Allergic (true) purpura.* Tremendous advance was made when Ackroyd demonstrated the presence of an immune mechanism in Sedormid®-induced purpura (1). In some unusually susceptible persons, Sedormid® apparently combines with platelets, causing them to become antigenic. This is a well-documented example of a relatively simple chemical compound that can alter body protein so effectively that it is recognized as foreign to the host. Of essence in this reaction is the combination of the drug as a hapten and the platelet's protein. The reaction requires the continued presence of Sedormid®, whether in vitro or in vivo. The linkage is not stable, and the individual variation in this stability probably explains why only a few persons exposed develop thrombocytopenia. Lysis of the platelets occurs when sufficient antibodies are formed to react with the platelet-Sedormid® antigen in the presence of complement. It has been hypothesized that the vascular endothelium, platelets and megakaryocytes are antigenically related (2). If true, it would be expected that the vascular endothelium might be concomitantly involved. The drug may combine with the endothelial cell, and a similar antigen-antibody reaction occurs which then results in nonthrombocytopenic purpura. This mechanism is not restricted to drug reactions but may be true also for the purpuras that follow infection. Since Ackroyd's original work, thrombocytopenia involving a similar mechanism has been demonstrated for other drugs, including quinine, quinidine and aminopyrine. Platelet antibodies have been demonstrated in both man and experimental animals. Positive patch tests, producing local purpura, in vitro platelet agglutination and a clot inhibition test can be demonstrated (7).

2. *Hemolytic anemia caused by drugs.* In most instances, drugs cause hemolytic anemia by a direct toxic action on

the red blood cell, that is, the drug or a metabolite of it interferes with cellular enzyme systems. The type of reaction occurring regularly is related to dosage. There are exceptions to this, exemplified by the acute hemolytic anemia that occurs in about 10% of Negroes given primaquine. The older cells of the red corpuscles are particularly sensitive to hemolysis induced by the toxic effect of the antimalarial drug. A similar mechanism of hypersusceptibility may explain the hemolytic anemia in patients treated with acetanilid, sulfanilamide and phenylhydrazine. Primaquine-sensitive cells also are excessively sensitive to these agents when tested in vitro.

Antibodies rarely have been demonstrated in drug-induced hemolytic anemia. Recently, an "immuno-hemolytic" anemia has been determined to be caused by quinidine, Fuadin® and Mesantoin. Antibodies have been demonstrated and the action is similar to that involved in Sedormid®-induced purpura. Evidence indicates that the drug links with the red blood cells and the complex becomes an antigen. An antibody to this loosely linked complex is formed which can cause lysis or agglutination of the cells. Although this mechanism has not been documented frequently, its presence may not have been eagerly sought for in other drug-induced hemolytic anemias.

Whereas the drug-induced hemolytic anemias are normocytic, some therapeutic agents such as Dilantin® and Primidone can induce a megaloblastic anemia. Megaloblastic anemia also occurs with the use of antifolic acid drugs in the treatment of leukemia. It is not known how these anticonvulsants produce anemia, although it is possible that they affect deleteriously a particularly susceptible enzyme system concerned with the maturation of red blood cells. No disturbance in vitamin B_{12} metabolism has been demonstrated.

GRANULOCYTOPENIA.—Similar mechanisms are involved also in granulocytopenia following aminopyrine therapy, associated with leukocyte agglutinins (17). Most drug-induced granulocytopenias are the result of direct toxic effect on the white blood cell or its precursors. Nitrogen mustard and 6 mercaptopurine (Purinethol®) are examples. Other drugs affect only a few persons who apparently are hypersensitive to the ordinary dosage. Included are sulfanilamide, novobiocin, chloramphenicol, many of the anticonvulsants and some of the antithyroid drugs.

APLASTIC ANEMIA.—The mechanism of aplastic anemia that complicates drug therapy is equally as obscure as that of the other dyscrasias. Chloramphenicol, the anticonvulsants and methylmercaptoimidazole (Tapazole®) are among the known causes. Aplastic anemia, iatrogenically induced by x-ray, urethan, Triethylene Melamine and the antifolic acid compounds used in the treatment of leukemia and lymphoma, is accompanied regularly by marrow hypoplasia, but this condition is usually an expected risk in critically ill patients. These toxic drugs are misused all too frequently. The incidence of aplastic anemia is evidently decreasing, since toxicities have been recognized more widely and drugs used with greater caution. It is particularly difficult to determine the incidence of reaction to a drug which adversely affects the bone marrow, because a similar effect caused by the underlying disease often cannot be distinguished. As soon as the aplastic anemia induced by chloramphenicol was recognized, more and more cases were reported. It has not been shown that the incidence of aplastic anemia has increased since the introduction of chloramphenicol; however, this fact should not be misinterpreted as indicating a lack of causal relation. There is no question that a significant number of patients who have developed aplastic anemia have received chloramphenicol and no other drug. When aminopyrine was used excessively, patients with agranulocytosis were frequently seen on hospital wards. Relatively more aplastic anemia, rather than agranulocytosis, was seen when aminopyrine was no longer used and chloramphenicol was abused. Much less chloramphenicol has been used during the past 2 years, and phenylbutazone has appeared as a major cause of granulocytopenia.

OTHER REACTIONS.—Leukemoid reactions are well recognized as a concomitant of sulfonamide therapy. Leukemia has occurred sequentially with the use of sulfonamides as well as chloramphenicol (20). In these instances, the relation has been based on single clinical observations and should not be interpreted as having more than chance significance.

There are frequent reports of clinical syndrome resembling infectious mononucleosis in patients who have received para-aminosalicylic acid for treatment of tuberculosis. The heterophil agglutination test is negative. It is likely that the syndrome represents a hypersensitivity to the drug.

Alimentary Tract

Although this pathway, from oral cavity to anus, suffers more than any other system in response to therapeutic agents, only brief attention will be paid to it. Most adverse effects are caused by direct irritation or toxicity on the mucosal surface, although anorexia, nausea and vomiting induced by many drugs reflect central nervous-system stimulation. The mucosa, as a body surface, has the potential to be sensitized by drugs and, occasionally, this is significant. More often, severe drug effects are the result of a combination of several factors, including direct toxicity, disturbed and altered flora, vitamin deficiencies and, perhaps, hypersensitization. The pseudomembraneous ulcerative colitis that can follow antibiotic therapy is an extreme example wherein all these mechanisms may play a role. However, none can be incriminated singly.

DIAGNOSIS OF TOXIC OR ALLERGIC REACTION

As has been indicated, the diagnosis of a toxic or allergic reaction caused by a drug is of great importance. It will frequently clarify an otherwise difficult diagnostic problem; at times, minimize serious morbidity and, occasionally, save life. Contrarily, a misdiagnosis of a drug reaction where none exists will have the opposite effect and may deprive the patient of a valuable and, at times, a life-saving medication.

Fortunately, the clinical syndromes caused by excessive dosage, intolerance or idiosyncrasy to most agents are characteristic and can be recognized by the informed and alert physician. Confirmation in these reactions can be obtained by lowering the dose or discontinuing the drug. If any question arises, and the symptomatology is not grave, it is wise to confirm idiosyncrasies with a provocative course.

The diagnosis of drug-induced allergy is somewhat more difficult, because other allergens may produce the syndrome. Moreover, many infections have lesions similar to those of drug allergy as part of the clinical course. The rashes of measles and scarlet fever, urticaria in infectious hepatitis and the polyarthritis of rheumatic fever are only a few of many examples. The diagnosis of drug fever without concomitant findings is most difficult. Even in these cases there

are usually enough clinical clues to make a fairly accurate diagnosis. The fever of sulfonamide and penicillin reactions often develops in a "stair-step" fashion. The conjunctivitis accompanying the morbilliform rash caused by the sulfonamides has more inflammation of the lateral and less of the medial half of the visible sclera than does measles.

In allergic reactions, the response to discontinuing the drug may be prompt, as it usually is in sulfonamide reactions or slow, as in penicillin and serum reactions, particularly in the serious blood dyscrasias. In fact, many patients with aplastic anemias never recover. Tests for antibodies may be tried in vitro. Simple precipitin or complement fixation tests in which the drug is used as an antigen are rarely successful. Coupling the drug chemically to proteins or to colloidal particles, such as colloidin, also has not been successful enough to make a practical test. In the hematologic reactions, if the drug is added to the cells or platelets in the presence of the patient's serum, agglutination and, if complement is present, lysis will indicate the presence of antibody.

In contact dermatitis the patch test, by its very nature, may be most helpful. Other than this, skin tests have not been of much use. Many drugs have almost consistently failed to give a positive test after intracutaneous injection in patients at the time of or following a reaction. Except for penicillin and serum, the frequency of false positive and negative skin tests is not well documented. With both these substances, the skin test is most useful in trying to determine the patients who may react with anaphylaxis. However, after being tested with these agents, some patients with negative intracutaneous and/or conjunctival tests still have developed anaphylaxis. Moreover, patients have reacted with fatal collapse to intracutaneous or conjunctival administration of small amounts of both these agents. For this reason it is probably best to do the less sensitive scratch test first and if it is negative follow it with the other tests. For confirmatory purposes in special patients, the passive transfer of serum may be used to avoid the risk of testing the patient directly. Because of the potential transmission of serum hepatitis, it is best to use this only for selected patients and in recipients who understand and are willing to accept the risk.

FACTORS PREDISPOSING TO DRUG REACTIONS

An understanding of some factors that influence the incidence of drug reactions, particularly those of allergic origin, will aid in the design of patient management and keep the incidence to a minimum.

Host Factors

Age.—It is well known that the reduced homeostasis potential of the elderly makes drug intolerances and idiosyncrasies more likely. Also, such reactions are frequent in infancy, but allergic reactions in infants are rare. The incidence of allergic drug reactions in children, especially to the sulfonamides and penicillin, is less than in adults. It must be remembered that sensitization may begin in childhood only to be manifested when the drug is given at a later time.

Heredity.—Genetic differences are of considerable importance in the response of any person to environment. Except for atopy and primiquine reactions, little is yet known of genetics and drug susceptibility. However, the primiquine study will no doubt give great impetus to further investigations of heredity where drug idiosyncrasy or intolerance is apparent but unexplained.

Atopy.—It is generally agreed that persons with atopic disease or history react more violently to the immediate-type allergic drug reaction. That the actual incidence of such reactions is greater has not been sufficiently demonstrated. In a study by one of us (13), the data indicated that atopic persons are more likely to react to penicillin. Not all other investigators have confirmed this finding. It is also questionable whether a family history of atopic disease has significant correlation with the occurrence of drug allergy. Although it may be true that an atopic person is predisposed to certain types of drug reactions, this does not mitigate the fact that most reactions are in nonatopic patients. It is often stated that a large segment of population, perhaps 10% for penicillin and 20% for sulfonamides, has a "proneness" to become sensitized. Within the 10%, there is a great variation in susceptibility, and atopic individuals seemingly are among the more susceptible. It is evident from the experience with horse serum that most persons can be sensitized

if sufficiently exposed. This does not indicate, however, that all such sensitized persons are capable of reacting to other allergens in the usual doses.

RACE.—That there may be a genetic predisposition of a racial group to react to certain drugs such as primaquine has already been stated. Data on the relative frequency of drug allergy in the different races does not show a real difference. In our study of penicillin reactions, the incidence was slightly lower in Negroes, but the difference was not significant.

SEX.—No signifiant differences are determined by sex in the response of experimental animals to antigenic stimuli. The higher incidence of blood dyscrasias in women following the administration of aminopyrine and chloramphenicol may be explained by their more frequent use of these drugs. In the same study of penicillin reactions, noted previously, the rate was somewhat higher in males, but again the difference was not significant.

ALTERED HOST REACTIVITY.—Chloramphenicol is effective in producing a greater incidence of bone-marrow depression in malnourished dogs (21). Chlortetracycline therapy has induced pellagra in malnourished persons. Both are examples of complex ecologic disturbance induced by drug therapy. Bacitracin and polymyxin B have greater toxicity when renal impairment is present. Most potentially toxic drugs that are metabolized in part by the liver or excreted by the kidneys are most hazardous when either organ is functionally impaired. Inflamed skin is predisposed to facilitate sensitization to drugs, either topically or systemically applied.

DRUG FACTORS

Structural configuration and its relevance to drug reactions has been discussed. In general, drugs with greater chemical reactivity are more capable of sensitizing. This may result in part from a greater affinity for tissue proteins that subesquently are altered and thereby enabled to induce sensitization. Penethamate (Neo-Penil®), a now-discarded penicillin preparation with an usually strong tissue affinity, was associated with an inordinately high incidence of severe allergic reactions. The sulfonamides that contain the benzene ring with attached NH_2 group are relatively antigenic. There

are structural differences within the group that evidently are of additional antigenic significance. Sulfathiazole is no longer used because of the frequency and severity of reactions. Sulfathiazole binds to tissue proteins with greater tenacity than do some of its less toxic analogues. In a group of patients treated with equal doses of five different sulfonamides for a similar period, those treated with sulfathiazole had a significantly higher incidence of reactions compared to those treated with its closely related analogues (Table 3). Tissue

TABLE 3.—FREQUENCY OF REACTIONS IN PATIENTS TREATED 5–15 DAYS WITH VARIOUS SULFONAMIDES USED IN THE SAME DOSE SCHEDULE (4–6 GM. STAT. AND 6 GM. DAILY)

DRUG	NO. PATIENTS	NO. REACTIONS	% REACTIONS
Sulfadiazine	289	9	3.1
Sulfamerazine	193	9	4.7
Sulfamethazine	30	2	6.7
Sulfathiazole	152	20	13.2
Sulfapyridine	192	7	3.7

affinity as determined by structural configuration is not, of course, the sole factor that determines reactivity. Other significant characteristics, such as specific organ localization, elimination and solubility have been alluded to previously.

ROUTE OF ADMINISTRATION.—Drug reactions can follow any route of feasible administration, although there are considerable differences. The topical route should rarely be used, as both the skin and mucous membranes are easily sensitized, and this method may result in potential systemic reactivity as well. Some simple chemical compounds maximally induce sensitization where applied directly to the skin or where given intradermally. Drug-induced anaphylaxis occurs most commonly after the intravenous and intramuscular injection of penicillin; however, it has followed oral and topical administration as well.

The tetracycline analogues, widely used, are similar in structural configuration. They are rarely associated with allergic reactions. This may be explained in part by their predominantly oral use.

PRESENCE OF ADJUVANTS.—Many simple chemical compounds which by themselves are incapable of inducing hypersensitivity are able to do so when combined with adjuvants such as mineral oil, falba, and the tubercle bacillus. Penicillin has been known to cause a greater incidence of un-

toward allergic reactions when combined with oil and beeswax (13). The apparent enhancing effects of adjuvants may result from the production of a greater antibody response in addition to prolonging absorption and elimination. The majority of anaphylactic reactions to penicillin have been reported after the use of procaine penicillin. It is unlikely that the relatively frequent incidence of anaphylaxis following the administration of procaine penicillin is caused by procaine sensitization, although this does occur.

DOSAGE AND DURATION OF TREATMENT.—Although drug intoxication is differentiated from allergic reactions by a close correlation between dosage and toxicity, there is a modified graded response between dose and sensitization and elicitation of reactions by antigens. A larger dosage of penicillin reportedly gives impetus to a greater reaction rate (5, 13). Higher and more sustained tissue levels that result from larger dosages may give greater opportunity for antibody formation. It is reported that the incidence of sensitization reactions to some sulfonamides increases in proportion to the dosage and its tissue concentration (12). However true it may be that total dosage is recognized as a significant factor both in facilitating sensitization and eliciting a reaction, this should not be misconstrued as indicating that small doses are safe. Any drug capable of evoking a reaction can do so in minute quantity. As a pertinent example, severe reactions have followed penicillin skin tests where small fractions of one unit have been injected.

The total duration of drug administration is apparently of greater significance than dosage in conditioning the incidence of an allergic reaction. Blood dyscrasias to chloramphenicol are known to occur more frequently in patients treated with repeated courses over long periods. Allergic reactions to streptomycin are much more common when it is used for a long period. Hypersensitivity reactions are relatively frequent in patients treated for tuberculosis as contrasted with those given streptomycin for acute illnesses. In a large series of servicemen receiving benzathine penicillin G, there was a reaction rate of 3.5% after 1 injection and 6% after either 4 or 6 injections (25). Table 4 derived from data obtained in our studies illustrates the significance of duration of treatment contrasted with dosage. After 6-15 days' treatment with both sulfonamides, the reaction rate was higher with larger doses, but after 15 or more days of uninterrupted

TABLE 4.—FREQUENCY OF CUTANEOUS AND/OR SYSTEMIC REACTIONS TO SULFAMERAZINE AND SULFADIAZINE RELATED TO DOSE AND DURATION OF TREATMENT

DRUG AND DOSE	DURATION OF TREATMENT			CUMULATIVE PERCENTAGE
	1-5 days R/pts.* %	6-15 days R/pts. %	over 15 days R/pts. %	
SULFAMERAZINE				
<2 Gm. stat. and <2 Gm. daily	0/183 0	3/100 3.0	4/30 13.3	16.6
2-6 Gm. stat. and 2-6 Gm. daily	3/286 1.0	7/161 4.4	3/35 8.4	13.8
>6 Gm. stat. and >6 Gm. daily	0/96 0	5/59 8.5	3/24 12.4	20.9
SULFADIAZINE				
<2 Gm. stat. and <2 Gm. daily	1/128 0.8	1/70 1.4	5/28 17.9	20.1
2-6 Gm. stat. and 2-6 Gm. daily	2/486 0.4	8/259 3.1	12/90 13.3	16.8
>6 Gm. stat. and >6 Gm. daily	1/378 0.3	10/201 5.0	4/40 10.0	15.3

*R/pts. = total reactions/total patients

therapy, the reaction rate did not show this correlation with dose. More striking and consistent with both drugs and for each dosage schedule was the marked increase in the percentage of reactions with duration of continuous treatment.

A question often asked about the method used and frequency of drug reactions concerns the significance of multiple therapeutic courses. The problem is difficult to answer,

TABLE 5.—Frequency of Reactions in Patients Treated 10 or More Days Continuously, Compared with Multiple Courses for a Total Duration of 10 Days or More, with Intervals of 7 Days to 6 Months

	Sulfadiazine	Sulfamerazine	Sulfathiazole
Single Course			
Number of patients	587	365	206
Number of reactions	78	53	40
Per cent reactions	13.5	14.5	19.4
Reactions on first day of second course			
Number of reactions	5	4	6
Per cent of patients	6.3	2.5	13.9
Reactions in later courses or later in second course			
Number of patients	80	158	43
Number of reactions	10	18	12
Per cent later reactions	12.5	11.4	27.9
Total reactions in second or later courses			
Number of patients	15	22	18
Per cent	18.8	13.9	41.8

because it is not easy to separate the effects of dose and duration of treatment from the potential effect of the drug-free interval. Table 5 summarizes our data on this point. In these patients the total dose and elapsed time of drug administration for the single course were in the same range as summated values for the multiple courses. The total reaction rate was higher when multiple courses were given than when a single course was given for 2 of the 3 drugs. Much of the difference was accounted for by a small number of immediate reactions occurring with the first dose or on the first day of the second course. If these reactions resulted from sensitization by the first course, but the patient had not re-

acted sufficiently for a clinical diagnosis, little difference could be attributed to the fact that the drugs were given in multiple rather than in single courses. Data indicate the principal effect of the latter courses, apart from what would be expected from administering the same dose for the same period without interruption, was to demonstrate that a small number of people had latent sensitization from the 1st course.

Of prime importance, the incidence of drug reactions varies directly with their over-all use. Hypersensitivity reactions to sulfanilamide and aminopyrine are rarely seen today because of restricted use. Even though the incidence of reactions to tranquilizers as a group is apparently low, their widespread use will no doubt result in a plethora of untoward reactions. It should be realized that at least 50% of people in the United States have received penicillin. If we assume that 10% of these are potentially sensitized, it indicates that eight million persons are capable of reacting.

PREVENTION

Primary prevention is always preferable to treatment, and this is particularly true of drug reactions. Both the toxic and allergic type drug reactions are too often irreversible or occur without sufficient warning to curtail harmful effects. The course of acute necrotizing angiitis which can complicate sulfonamide therapy is little influenced by any therapeutic measure except that obtained by symptomatic relief. Again, anaphylactic shock often occurs rapidly and unexpectedly. Treatment is not likely to be available in time to be of benefit unless preparations can be made before drugs are administered. The deleterious effects of a drug can be precluded to a large extent by adhering to the principles of prevention.

To minimize the problem, co-operation is needed at all levels among those who are concerned with drug therapy. This includes everyone from the manufacturer to the patient himself. Research, education and restraint are needed at every level. Following is a summary of measures designed to offset present disadvantages of antibiotic drug therapy.

1. Analogues should be developed which have a wide margin between the therapeutic and toxic amounts, fewer

side actions and lower sensitizing potentials. This has been done in the past and must be continued.

2. Preliminary studies which are designed particularly to estimate human toxicity should be made before new drugs are released for general use. Such studies should be designed as an adequate sample of the population and be controlled against patient and observer biases.

3. In addition, advertisements which claim low toxicity for new drugs should be restrained until the drug has been used widely.

4. The individual investigator should co-operate by tempering enthusiasm for results obtained in small samples of the population.

5. More investigation should be concerned with measures designed to detect potential reactors. This necessitates basic research to develop new methods, in addition to application of existing procedures to new situations.

6. Physicians and dentists who operate at the practical level may effect many preventive measures:

(a) It is possible to detect reactors, usually in retrospect, by administering a provocative dose of a drug to elicit a similar reaction. This may satisfy the inquisitive nature of the physician but may be lethal to the patient and therefore is not advisable. A far more practical and fruitful means of detection is to take a careful, complete history of previous drugs received and possible reactions to them. This entails questioning beyond "have you had any drugs?" The drug case history is an area where "leading questions" such as the following are permissible: "What do you do for a headache?" "Have you ever received treatment for a cold?" "When did you last visit the dentist and were you treated?" Professional men can help one another by telling the patient the name of the drug he has received.

(b) A drug should be used only with clear indications, and alone whenever possible. The wise physician will hesitate to prescribe new drugs, if time-tested agents will accomplish his purpose. This is succinct but absolute!

(c) The physician should avoid topical applications to the skin and mucous membranes except where specifically indicated. This is particular important where the skin is already traumatized.

(d) Drugs designed for slow absorption should be avoided when feasible.

(e) A shorter single continuous course is preferable to repeated and long-term therapy where it is as effective.

(f) Dosage should not exceed that established by controlled studies as optimally effective, except under unusual circumstances.

(g) When possible, drugs should be administered orally. When the intramuscular method must be used in a patient suspected of being sensitive, the injection should be given in the lower part of the extremity, which would permit the use of tourniquet. The proper expectant medications to treat a reaction should be in a syringe ready for immediate use.

(h) Another medication of unrelated structure should be substituted where sensitivity to a drug is suspected. Penicillin O is not a completely satisfactory substitute for penicillin G, because cross-reactions occur.

(i) The physician also should be alert to the early signs of drug reactions and differentiate them, if possible, from the effects due to the disease itself. When this differential is not certain, the drug, and not the underlying disease, should be considered guilty. Although cessation of a drug, when early signs of toxicity become apparent, may alleviate further damage, too frequently the "horse is already out of the barn." Routine white blood cell counts are strongly recommended when using drugs that induce granulocytopenia, but unfortunately by the time leukopenia is manifested it is often too late to reverse the process.

(j) Measures should be taken to insure against the use of contaminated syringes. Unexpected reactions occur from using them.

(k) The use of antihistaminics, epinephrine, procaine and adrenocortical steroids has been suggested as a prophylactic method for inhibiting the allergic response to a drug. There is little if any justification or logic to such use. Antihistaminics have been shown to be effective in ameliorating the early urticarial reaction to penicillin but would not be expected to inhibit significantly delayed or severe reactions (15). Anaphylaxis is probably not prevented by these measures but may be masked and be manifested when the patient is no longer under careful observation.

(l) The patient should be informed when evidence or

likelihood of a drug sensitization exists. It would be well for the patient to have a written documentation of this for future reference.

7. Other professions should be encouraged to minimize the use of drugs that eventually may be taken by humans. Industrial use of antibiotics may well sensitize many workers. Drugs important to human medicine should be reserved for that purpose and other agents developed for the other uses.

8. Patients need repeated and continuous education as to the dangers of self-medication. The most important facet of this education is the example set by the medical profession. Lack of restraint leads to further lack of restraint.

TREATMENT OF DRUG REACTIONS

When a drug reaction occurs, the first step is to stop the drug and, when necessary, make a proper substitution. Elimination is sometimes possible by the use of specific agents. British anti-lewisite may be useful to eliminate heavy metals. More recently penicillinase has been found effective in treating some penicillin reactions. Therapy directed against the mechanisms that cause a reaction is the most suitable approach at the present time. The antihistaminics are useful adjuncts in a limited and specific group of allergic reactions of the immediate type, particularly those occurring within hours after the drug has been given. Antihistaminics are of benefit only in some patients with the late urticaria that accompanies serum sickness. The release of histamine is of less significance in the serum sickness type of drug reaction, and it should not be expected that antihistaminics would always be of direct "antagonistic" benefit. It has not been demonstrated conclusively that the antihistaminics directly antagonize histamine. They may exert their action by inactivating monamine oxidase, an enzyme that inactivates epinephrine. Their antihistaminic action is of no benefit in the delayed type of hypersensitivity, such as contact dermatitis. Moreover, they are of little benefit in the treatment of severe immediate reactions characterized by anaphylaxis, possibly because their administration cannot be accomplished rapidly enough. Anaphylaxis is most suitably managed by the use of epinephrine and 1-arterenol (Levophed®) to counteract bronchospasm and cardiovascular collapse. Oxy-

gen should be given if cyanosis persists. If the eliciting drug has been given intramuscularly or subcutaneously into an extremity, a tourniquet may be placed above the injection site and epinephrine injected locally to delay absorption.

The corticosteroids are effective in minimizing the inflammatory response in some hypersensitivity reactions. They do not inhibit directly the antigen-antibody reaction, although they may reduce antibody production by lympholysis. These steroids, as well as ACTH, are of particular benefit in severe, prolonged reactions, such as serum sickness and acute necrotizing angiitis. Serum sickness caused by drugs is usually not severe and can be managed without the added complications that accompany hormonal therapy. If pain exists, analgesics should be given, meperidine if necessary. The delayed type of urticaria and angioedema will be benefited by epinephrine. Erythematous and pruritic rashes may be symptomatically treated with starch or oatmeal baths, and sedatives may be used to ameliorate the symptoms.

REFERENCES

1. Ackroyd, J. A.: The cause of thrombocytopenia in Sedormid® purpura, Clin. Sc. 8:269, 1949.
2. Ackroyd, J. A.: Allergic purpura, including purpura due to foods, drugs, and infections, Am. J. Med. 14:605, 1953.
3. Becker, S. W., and Obermayer, M. E.: *Modern Dermatology and Syphilology* (2d ed.; Philadelphia, London, Montreal: J. P. Lippincott Company, 1947).
4. Beutler, E., Robson, M. and Buttenwieser, E.: The mechanism of glutathione destruction and protection in drug-sensitive and nonsensitive erythrocytes. In vitro studies, J. Clin. Invest. 36:617, 1957.
5. Chancey, R. L., *et al.*: Studies of streptococcal prophylaxis: comparison of oral penicillin and benzathine penicillin, Am. J. M. Sc. 229:165, 1955.
6. Committee on Nomenclature for the Association of Allergy Clinics of Greater New York: Definition of words pertaining to allergy, J. Allergy 12:202, 1941.
7. Freedman, A. L., and Brody, E. A.: Immunothrombocytopenic purpura due to quinidine, J. Lab. & Clin. Med. 48:205, 1956.
8. Knowles, H. C., Zeek, P. M., and Blankenhorn, M. A.: Studies on necrotizing angiitis, A.M.A. Arch. Int. Med. 92:789, 1953.
9. Kojis, F. G.: Serum sickness and anaphylaxis. Analysis of Cases of 6,211 patients treated with horse serum for various infections, Am. J. Dis. Child. 64:93, 1942.
10. Landsteiner, K., and Jacobs, J.: Studies on the sensitization of animals with simple chemical compounds, J. Exper. Med. 61:643, 1935.
11. Leake, C. D.: Drug allergies, Postgrad. Med. 17:132, 1955.

12. Lehr, D.: Lowered incidence of sensitization through use of sulphonamide combinations (a new concept), Brit. M. J. 2:543, 1948.
13. Lepper, M. H., *et al.*: Studies on hypersensitization to penicillin, J. Clin. Invest. 28:826, 1949.
14. Lewis, G. W.: Acute immediate reactions to penicillin, Brit. M. J. 1:1153, 1957.
15. Mathews, K. P., *et al.*: A controlled study on the use of parenteral and oral antihistamines in preventing penicillin reactions, J. Allergy 27:1, 1956.
16. Meyer, R. L.: Group-Sensitization to Compounds of Quinone Structure, in Kallos, P. (ed.), *Progress in allergy*, Vol. 4 (Boston-Toronto: Little, Brown & Company, 1955).
17. Moeschlin, S., and Wagner, K.: Agranulocytosis due to the occurrence of leukocyte-agglutinins (Pyramidon and cold agglutinins), Acta haemat. 8:29, 1952.
18. Mosko, M. M., Nejedly, R. F., and Rostenberg, A., Jr.; The significance of cutaneous reactions to penicillin, penicillium and trichophyton, Antibiotic Med. 1:125, 1955.
19. Motulsky, A. G.: Drug reactions, enzymes, and biochemical genetics, J.A.M.A. 165:835, 1957.
20. Mukherji, P. S.: Acute myeloblastic leukemia following chloramphenicol treatment, Brit. M. J. 1:1286, 1957.
21. Reutner, T. F., Maxwell, R. E., and Weston, J. K.: Antibiotics and the bone marrow of well-nourished and malnourished dogs, in Welch, H., and Marti-Ibanez, F. (eds.), *Antibiotics Annual* 1955-56 (New York: Medical Encyclopedia, Inc., 1956), p. 84.
22. Rostenberg, A., Jr.: The allergic dermatosis, J.A.M.A. 165:1118, 1957.
23. Rostenberg, A., Jr., and Brunner, M. J.: Remarks on theories of antibody formation, Ann. Allergy 8:108, 1950.
24. Rostenberg, A., Jr., and Webster, J. R.: Mechanisms of cutaneous drug reactions, especially to antibiotics, J.A.M.A. 154:221, 1954.
25. Sherwood, R. W., Gronbeck, C., and Denny, F. W.: Reactions from multiple injections of benzathine penicillin G, J.A.M.A. 165:667, 1957.

Published monthly by

THE YEAR BOOK PUBLISHERS, INC.

200 EAST ILLINOIS STREET

CHICAGO 11, ILLINOIS, U.S.A.

Annual Subscription—$9.00

Annual Student-Intern-Resident Subscription—$6.00 Prepaid

Permanent, attractive binder to accommodate 12 issues—$1.25

Change of address notice should be sent 60 days in advance to Disease-a-Month, 200 East Illinois Street, Chicago 11, Ill., to assure uninterrupted service.

These and Other Back Numbers Available to
New DM Subscribers
$1.25 each, postpaid

LEUKEMIA & LYMPHOMA (January, 1958)
Joseph H. Burchenal and *Henry D. Diamond*

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (February, 1958)
David Davis

CEREBRAL VASCULAR DISEASE (March, 1958)
Joseph M. Foley and *Simon Horenstein*

BRUCELLOSIS (December, 1957)
Abraham I. Braude

FEVER OF UNKNOWN ORIGIN (November, 1957)
Ivan L. Bennett, Jr., and *Edward W. Hook*


THE YEAR BOOK PUBLISHERS, INC.
yb
CHICAGO